Diffuse Intraductal Papillary Adenocarcinoma of the Pancreas

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The incidence of multicentricity in pancreatic cancer has been reported to be as high as 38%. Recent surgical and autopsy series have documented multicentric disease and the presence of carcinoma *in situ* in association with invasive carcinoma. Described are the clinical and pathologic findings in a 41-year-old woman who had total pancreatectomy for diffuse ductal transformation to papillary adenocarcinoma associated with a wide spectrum of extensive ductal epithelial changes. The significance of epithelial abnormalities as they relate to the occurrence of multicentric tumor is discussed, and the findings in this patient are compared with those of other distinctive clinicopathologic entities. Despite an apparently favorable outcome and 20-month disease-free follow-up in this patient, no good evidence indicates that age, extent of procedure, or lack of tumor invasion has prognostic significance in pancreatic cancer.

THE HISTOGENESIS AND NATURAL HISTORY of pancreatic ductal adenocarcinoma remain unknown. Whether the tumor has its origin in the various lesions found in association with it (*i.e.*, ductal epithelial metaplasia, nonpapillary hyperplasia, papillary hyperplasia, adenomatous polyps, or villous papillomas) is poorly understood and much argued.[1-6] In contrast, the significance of frank carcinoma *in situ* seems to be more generally accepted as that of a precursor lesion to invasive ductal cancer.[1,4] Although some authors[2] consider it likely that there is an evolution of epithelial changes from nonpapillary hyperplasia to papillary hyperplasia to atypical hyperplasia to carcinoma, others argue that this idea is speculative, that papillary hyperplasia is reactive in nature, and that marked atypia (severe dysplasia) seems to be a *de novo* precursor of ductal cancer.[1,4,6]

The concept that benign or reactive lesions may act as a setting conducive to the development of carcinoma helps to explain the occurrence of multicentric lesions in many cases of pancreatic ductal adenocarcinoma.[7-9] In such instances, multiple foci of carcinoma might arise in a "field lesion" consisting of reactive ductal epithelial change.[1,8]

The observations of multicentricity in pancreatic ductal cancer and of the presence of carcinoma *in situ* in association with invasive carcinoma have been features of several recent surgical and autopsy series[6,8-11] and have led to assertions that the poor prognosis of pancreatic ductal cancer may be related to multicentric disease. Operations that are more radical than the conventional Whipple procedure (pancreatoduodenectomy), such as total pancreatectomy, have been attempted in hopes of achieving an improved survival.[7,9,11,12] Survival has not improved, however, and even though multicentric lesions (including carcinoma *in situ*) have been described in approximately a third of patients in some reported series,[5,7,9,11] the clinical significance of this finding remains uncertain.

We report a patient in whom total pancreatectomy was performed for diffuse ductal transformation to papillary adenocarcinoma associated with a wide spectrum of extensive ductal epithelial changes.

Case Report

Clinical Findings and Treatment

A 41-year-old woman presented with abdominal discomfort and increasingly loose stools. She had not consulted a physician during the previous 5 years, and she admitted to a 3- or 4-year history of progressive diarrhea, with up to six large, greasy, foul-smelling bowel movements per day. Painless postprandial fullness and bloating were noted. Cholelithiasis had been diagnosed 5 years before admission after an episode of severe acute epigastric pain unaccompanied by fever or chills; ultrasonography had revealed many small gallstones, and an oral cholecystogram revealed a non-opacifying gallbladder. Operation was deferred at that time. She had no history of smoking or alcohol abuse.

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Submitted for publication: September 29, 1986.

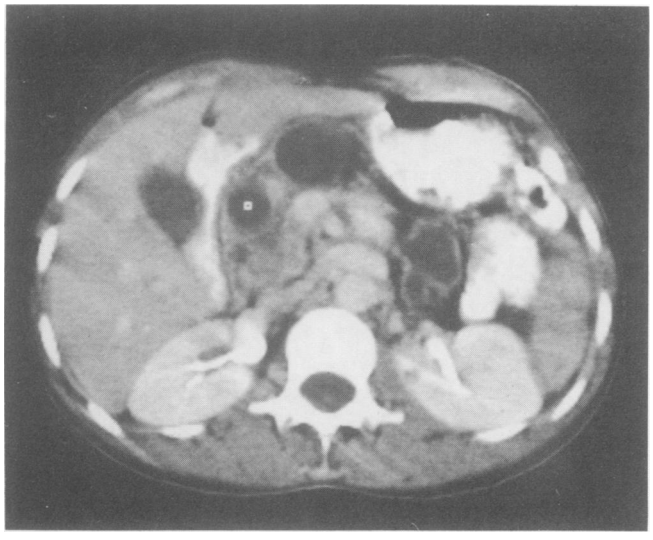


FIG. 1. Computed tomographic scan of abdomen reveals loculated, multicystic mass in region of pancreas.

Physical examination revealed an anicteric woman without ascites, abdominal tenderness, or a palpable mass. Her hemoglobin concentration was 11.4 g/dL, and the serum amylase value was 54 U/L. Abdominal ultrasonography showed a normal gallbladder and liver and the presence of multiloculated pancreatic cysts; no stones were revealed. A computed tomographic scan demonstrated a loculated mass at the head of the pancreas with multiple associated pancreatic cysts (Fig. 1).

The preoperative differential diagnosis included pancreatitis, ectasia, cystadenocarcinoma, or adenocarcinoma of the head of the pancreas with distal ductal involvement. At abdominal exploration the pancreas was noted to be firm and rubbery and to contain multiple cystlike lesions. No discrete tumor was palpated. Frozen sections of tissues obtained by transduodenal biopsy demonstrated an epithelial neoplasm believed to be of either ductal or islet cell origin. Total pancreatoduodenectomy with splenectomy was performed.

The postoperative recovery was uneventful, and the patient was dismissed on the 15th postoperative day. Evaluation 22 months later revealed no evidence of residual or recurrent tumor.

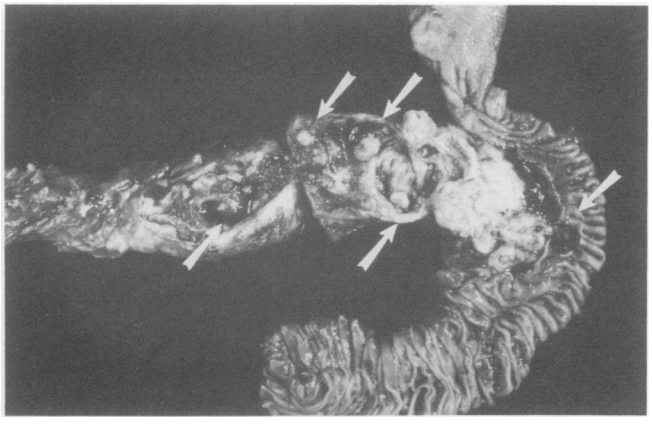


FIG. 2. Severe ductal ectasia and multiple nodules of papillary adenocarcinoma (*arrows*) are present throughout pancreas (opened posteriorly). Note presence of tumor nodule at ampulla.

Pathologic Findings

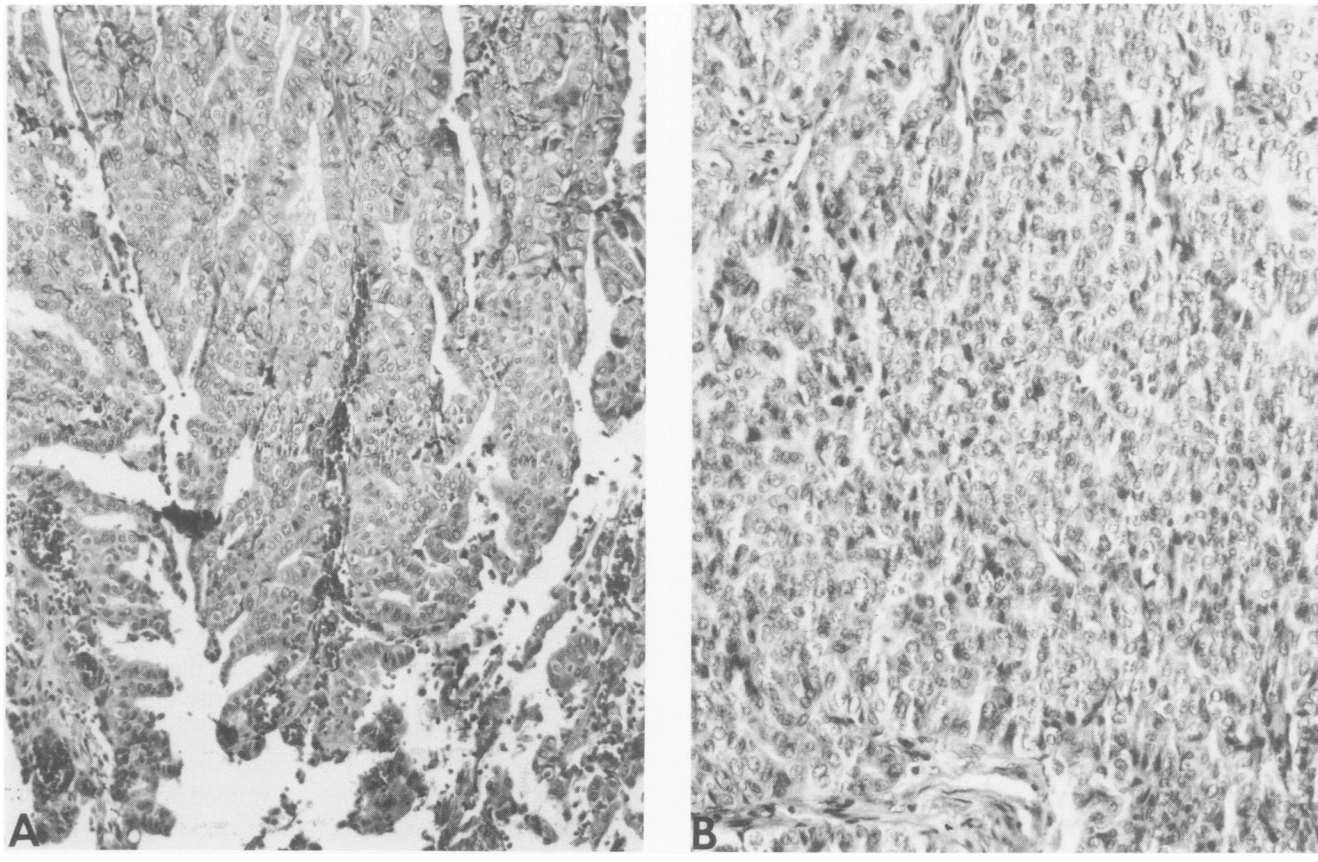
Gross examination of the specimen revealed a 22 × 3 × 2 cm pancreas with an attached unopened segment of duodenum and the spleen. On opening the intestine, a nodule of red-brown tumor, 1.5 × 1 × 1 cm, could be seen protruding into the duodenal lumen at the ampulla of Vater. The pancreas was sectioned along the duct (Fig. 2). The main pancreatic duct was severely ectatic, 1–3 cm in diameter, and studded with small nodules of papillary tumor throughout its length.

Well- to moderately differentiated papillary adenocarcinoma involved the ampullary region and most of the pancreatic duct microscopically (Fig. 3). Microscopic epithelial abnormalities included nonpapillary hyperplasia, papillary hyperplasia, atypical hyperplasia, and carcinoma *in situ* (Fig. 4), as well as papillary and solid regions of adenocarcinoma. Occasional psammoma bodies were present. Microfoci of periductal extension were noted (Fig. 5). Nine pancreatoduodenal and six peripancreatic lymph nodes were reactive.

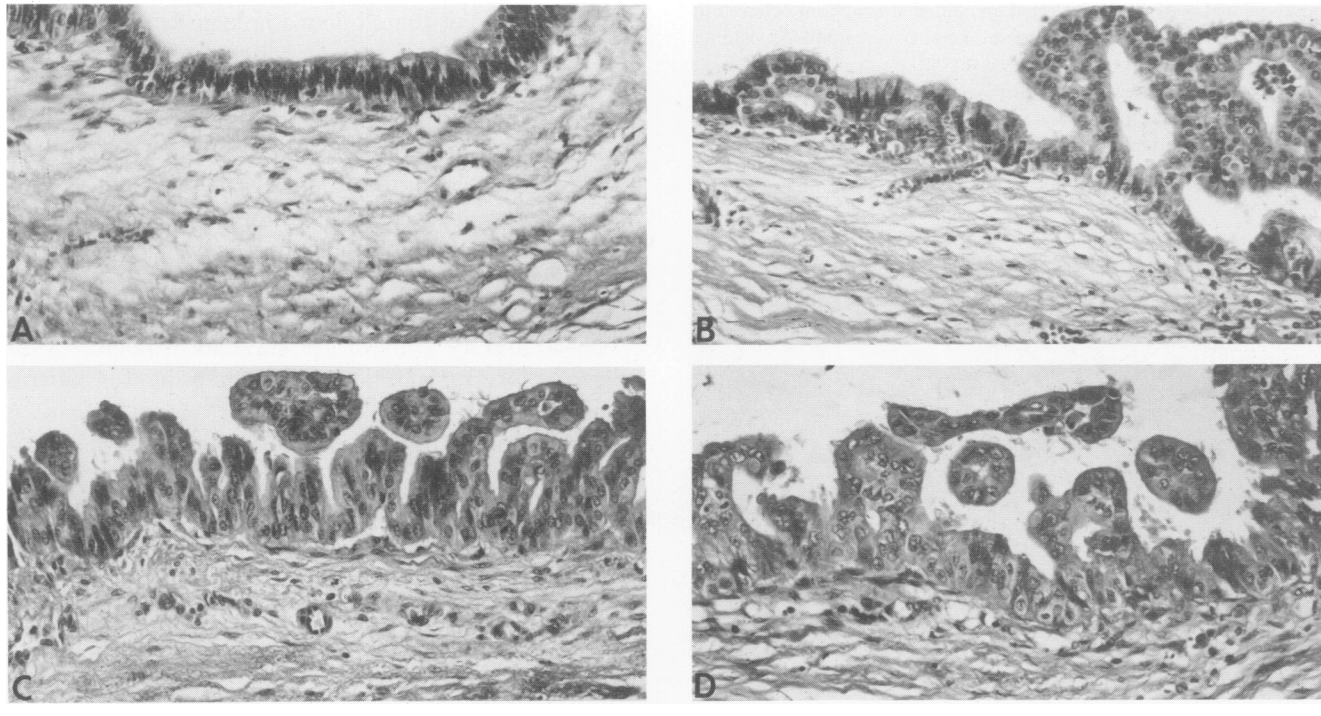
Discussion

Papillomatous transformation of the pancreatic ductal system with multicentric carcinoma *in situ* was described by Habán[13] in the German medical literature 50 years ago. The author had been impressed that the malignant alterations witnessed in the pancreatic ductal epithelium of three elderly women appeared to arise in the setting of an extensive, regenerative papillary epithelial process. More recent echoes of such observations were found in five cases of carcinoma *in situ* studied by Cubilla and Fitzgerald.[8] We have documented, in a much younger patient than has been previously described, a case of multicentric pancreatic papillary carcinoma, invasive as well as *in situ,* that occurred in conjunction with various epithelial changes suspected to be transformational stages leading to cancer.

Comparison of the clinicopathologic features in this case with those of mucinous cystic tumor (cystadenocarcinoma) is not unreasonable, although the pathologic features of the latter are fairly characteristic and do not resemble those of the tumor in our case. Initially considered to be either benign or malignant on the basis of histologic appearance, mucinous cystic tumor is now generally recognized as intrinsically malignant, or at least as having sufficient potential for malignancy that it should be so regarded. Clinically, patients present most commonly between 40 and 49 years of age; 85% are women.[14] Postoperative survival is notably longer than that for patients with pancreatic ductal carcinoma.[8,14] Most mucinous cystic tumors are located in the tail of the pancreas. Well-circumscribed, comprising multilocular or unilocular cysts, having an average diameter of 10.5 cm, and featuring a dense fibrous wall, the tumors contain thick mucoid fluid; microscopically, the cystic spaces are lined by mucin-producing columnar epithelial cells. A range of epithelial changes may be found throughout the tumor, often in the same microscopic field, and these have been described as the most notable microscopic feature of the neoplasm as well as a pitfall in histologic diagnosis.[14]



FIGS. 3A and B. Appearance of well-differentiated papillary adenocarcinoma (*A*) as seen throughout length of pancreatic duct; small portions showed solid pattern of growth (*B*). (Hematoxylin and eosin; *A*, ×150, *B*, ×235.)



FIGS. 4A–D. Spectrum of ductal epithelial changes included nonpapillary hyperplasia (*A*), papillary hyperplasia (*B*), atypical hyperplasia (*C*), and carcinoma in situ (*D*). (*A–D*, hematoxylin and eosin; ×180.)

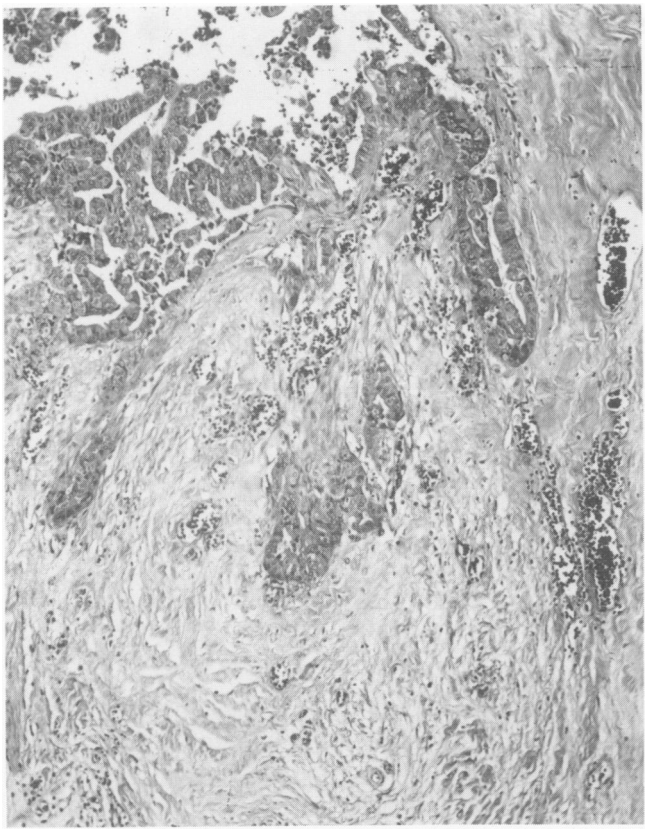


FIG. 5. Multiple sections of all regions of pancreas revealed only microfocal periductal extension of tumor. (Hematoxylin and eosin; ×90.)

Ductal adenocarcinoma, in contrast to mucinous cystic tumor, is typically located in the head of the pancreas, has an average diameter of 5 cm, is confined to the pancreas in a minority of cases, and shows a peak occurrence during the seventh decade of life.[8] Rarely are women age 40 years or younger affected.[11]

The incidence of multicentricity in pancreatic cancer has been reported to be as high as 38%.[9] Series of pancreatectomy specimens that have been thoroughly studied are few;[5,9] to our knowledge, extensive serial sectioning after resection for ductal cancer has not been performed to the degree necessary for accurate topographic documentation of microscopic ductal epithelial changes or for assessment relative to the development of neoplasia.[1]

The results of operation for patients with pancreatic carcinoma are unpredictable. Despite the apparently favorable outcome in our patient, we have no good evidence that age, extent of procedure, or lack of tumor invasion has prognostic significance. A slight prognostic advantage in pancreatic carcinomas of a papillary nature has been discerned by others.[15] In general, the only sound prognostic factor seems to be the pathologic type of lesion encountered.

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